A Population Approach to the Rational Use of Therapeutic Interventions

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THE EVIDENCE BASE

Most developed countries, and an increasing number of developing ones, aspire to provide universal access to healthcare for their citizens. All, however, have resource constraints and must inevitably make priorities in determining their coverage decisions. Consequently, when making decisions about the availability of therapeutic interventions both cost effectiveness, as well as clinical effectiveness, must be taken into account by decision-makers.[1]

Clinical Effectiveness

The evidence supporting the clinical effectiveness of a therapeutic intervention may be either experimental (ie, based on the results of randomized controlled trials), or observational in character.[2] Some national and international advisory bodies have developed "hierarchies" of evidence that give unreasonable prominence to randomized controlled trials in their evaluation of the clinical evidence supporting the use of particular interventions. As I have argued elsewhere[2] it is not the method itself that is of importance, but whether the particular method is appropriate to answer the specific question that is posed. Moreover, modern decision-analytic techniques often involve combining the results from experimental and observational study designs[3] and which hierarchies are incapable of accommodating.

Appraising the clinical effectiveness of a therapeutic intervention, for populations, also involves evaluating its effectiveness in comparison with alternatives, including where there are no active treatments, for best supportive care.[3] Identifying appropriate comparator interventions, in conditions for which treatments are already available, often poses problems for decision-makers. Confining such "active comparators" only to those that are licensed for treating the same condition is often inappropriate. Many established treatments (dexamethasone for the treatment of multiple myeloma is just one of numerous examples) have never been licensed for the purpose despite being in widespread use; and in pediatrics "off-label" prescribing is, of necessity, very common. Reference to published clinical guidelines may be of some assistance but, since few of these take cost effectiveness into account, their usefulness may be limited. Advice from relevant experts on what constitutes "current best practice" may be of value but anything approaching a consensus is often difficult to achieve. In practice, most decision-makers use a combination of approaches although their conclusions are often contentious.

Having decided on the most appropriate comparator(s), decision-makers must then determine the best approach to a quantitative comparison. Ideally they will have access to the results of one or more direct comparisons between the new intervention (intervention A) and the chosen comparator (intervention B). In reality, such direct comparisons are often unavailable and decision-makers must rely on either indirect, or mixed treatment, comparisons.[3] Indirect comparisons involve using the results of placebo-controlled studies (placebo versus intervention A, placebo versus intervention B) and estimating the difference between intervention A versus intervention B by imputation.[4] Mixed treatment comparisons involve combining the

Decisions about the rational use of therapeutic interventions in populations require a robust approach to the evaluation of the underpinning evidence. Additionally, however, decision-makers must exercise judgement.

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results of direct and indirect comparisons in a network model.[5]

Cost Effectiveness

The economic evaluation of an intervention involves estimating its incremental (additional) costs and benefits compared with those of one or more of the appropriate comparators (including, where appropriate, best supportive care). The incremental costs divided by the incremental benefits yields the "incremental cost effectiveness ratio" (the ICER).[3]

The incremental costs obviously include the acquisition costs of the intervention. They will also include the costs of extra monitoring requirements (such as extra blood tests or X-rays) and any additional medical or nursing time needed. The cost calculations should also incorporate the consequences of the management of any adverse effects. The incremental costs will be reduced if the use of the intervention is associated direct savings (sometimes known as "cost offsets") to the healthcare system.

Depending on the economic perspective to be used, the evaluation may incorporate indirect costs or savings arising from so-called "productivity" gains or losses.[3] These might include the savings from less time off work or the costs arising from the need to employ temporary help in the home. They might also include the cost to society more broadly in providing welfare services such as sickness or unemployment benefits.

The scope of the economic perspective is a political, rather than a scientific, decision. The Statutory Instruments creating the National Institute for Health and Care Excellence (NICE) currently oblige it to confine its perspective to costs and savings to the healthcare system although this may change in the future. Other countries (such as Sweden) take a broader – societal – economic perspective. Although seemingly logical a societal perspective may impose an additional degree of uncertainty in its calculation; and has the potential to disadvantage children and the elderly because neither contributes financially to an economy. Furthermore, in the absence of full employment, the net costs and savings to public funds will be zero because as one person loses their job due to ill health an unemployed person joins the workforce.

Most economic analyses express the benefits of therapeutic interventions in the form of cost utility analyses. In this, the benefits are expressed as the gain in the quality of life multiplied by the time for which it is enjoyed. This yields the "quality of life year gained" or "QALY". The gain in the quality of life produced by an intervention is assessed using a generic instrument such as the EuroQual-5D.[6] In this, the quality of life is expressed as a change in health utility on a scale between 0 = dead and 1 = full health. Using this scale, for example, a hip prosthesis for osteoarthritis gives an increased utility of 0.3; and, since hip prostheses are on average "enjoyed" by recipients for 15 years, the QALY gained is 0.3 x 15 = 4.5. If the cost of a hip

Table. A selection of incremental cost effectiveness ratios (ICERs) from NICE's technology appraisals programme

Intervention	Indication	ICER (£ per QALY gained)
Alendronate	Primary prevention of osteoporotic fractures	9000
Rituximab	Aggressive non-Hodgkins lymphoma	10,500
Etanercept	Severe psoriasis	14,500
Trastuzumab	Early breast cancer	18,000
Dabigatran	Stroke prevention in atrial fibrillation	18,900
Golimumab	Severe ankylosing spondylitis	27,000
Bortezomib	Multiple myeloma	32,500
Pemetrexid	Malignant mesothelioma	34,500
Imatinib	Chronic myeloid leukaemia	36,000
Riluzole	Motor neurone disease	40,000
Sunitinib	Advanced renal cancer	55,000

prosthesis (including all the direct costs) is £5000, then the ICER – at its crudest – is £5000 ÷ 4.5 = £1100 per QALY gained.

The advantage of cost utility analysis is its universality. Because the benefits are expressed as a change in health utility (derived from the EuroQol-5D) the cost effectiveness of one intervention, for the treatment of one condition, can be directly compared with the cost effectiveness of another intervention for an entirely different condition. This point is illustrated in the Table which shows a sample of ICERs, taken from NICE's technology appraisals programme, for a number of interventions, across very different indications.

Calculating the ICER is of limited value for decision-makers without defining a "threshold" distinguishing cost effective, from cost ineffective, interventions. Various approaches have been proposed to identify the point at which a particular ICER imposes an intolerable opportunity cost to a healthcare system. They include:

1. Listing all the interventions that could be used by a healthcare system, in ascending order, and defining the threshold as the point which the healthcare budget is exhausted. The problem with this approach is that there is no reliable evidence base upon which such a list could even begin to be produced.
2. Enquiring, from members of the public, what they are "willing to pay" for improved quality of their healthcare. Although this method has been applied to other fields (such as transport economics) its appropriateness in a tax-funded system, such as the UK's National Health Service, has been questioned.
3. Examining overall expenditure patterns for various disease groupings and impute a cost effectiveness threshold. Critics of this method suggest that it assumes all current healthcare expenditure is cost effective.
4. The suggestion by the World Health Organization that the threshold should be a function of a country's per capita gross domestic product (GDP). Using this measure they suggest that an ICER of less than a nation's per capita GDP should always be regarded as cost effective; and that an ICER of more than three times per capita GDP should invariably be considered to be cost ineffective. Although it seems intuitively appropriate to link cost effectiveness thresholds to per capita GDP the basis for the upper and lower limits are unclear.
5. Inferring a threshold, as with NICE, from previous decisions. Based on its early experience NICE has adopted a threshold range of £20,000 to £30,000 per QALY gained which is largely based on the collective judgement of the UK's health economists. Curiously, or perhaps coincidentally, this is similar to the thresholds suggested by extrapolation from the approaches described in 2), 3) and 4) above.

DECISION-MAKING

Whether, or not, an intervention should be available in a particular healthcare system requires not only careful consideration of the evidence but also requires for judgements to be made. These judgements fall into two types – scientific judgements and social value judgements[7].

Scientific Judgements

Scientific judgements are required to interpret the science that underpins the evidence base[7]. The evidence is never perfect and there is always be additional information that decision-makers might wish to see before drawing their conclusions; but insisting on "perfect information" would prevent them from ever making any decisions at all. Decision-makers must therefore make judgements. These typically involve resolving three questions[3]:

1. *How reliable is evidence for effectiveness?* The answer will require scrutiny of the design of the studies on which the evidence is based, the endpoints used in the assessment of likely efficacy, and the approach that has been taken in evaluating the impact of the intervention on the quality of life. Relying on hierarchies of evidence is no substitute.[2,3]
2. *Are the results generalizable to the wider population in whom the intervention is likely to be used?* When new pharmaceutical products are introduced, their effectiveness will have been studied in relatively small homogeneous populations. Effectiveness in older people, those with a range of co-morbidities, and for prolonged periods of time, may be uncertain.
3. *Is it appropriate to limit an intervention's use to subgroups of patients?* It is not uncommon for an intervention to be cost ineffective overall but cost effective in a specific subgroup of the population of potential recipients. Judgements have to be made about the appropriateness of what is often a *post hoc* subgroup analysis; as well as judgements about

the extent to which the members of such subgroups can be reliable identified in advance of starting treatment.

The expert members of appropriate advisory bodies – including clinicians as well as statisticians and economists – should be chosen to make such scientific judgements.

Social Value Judgements

Social values relate to the social sciences rather than to the clinical sciences.[7] They include issues such as whether an extra year of the life of children should be regarded as more valuable than an extra year of life of their grandparents; or whether it is appropriate for healthcare systems to pay premium prices for interventions used in the treatment of very rare diseases.

The members of conventional scientific advisory bodies have no legitimacy to impose their own social values on the healthcare systems for which they are responsible.[8] The manner in which such social values are elicited, and incorporated into decisions about availability and use of therapeutic interventions, varies between different jurisdictions. In some, social values are either implicitly, or explicitly, imposed by politicians (primarily health ministers). Others attempt to derive social values from the population. NICE has pioneered the use of a "Citizens Council", drawn from the general population, to establish the social values it should adopt in its appraisals of the use of therapeutic interventions in the UK's National Health Service.[8]

The social values that decision-makers must incorporate will depend, fundamentally, on the approach of the healthcare system to "distributive justice" .[3,8,9] This is the term used by political and moral philosophers in considering what is right, or just, in the allocation of goods within society. Three moral theories of distributive justice have a particular resonance for the allocation of resources in healthcare[9]:

1. *Libertarianism* is based on the premise that individuals should be able and expected to finance their healthcare through their own efforts; and that market forces should enable them to do so at a reasonable price. This approach underpins much of the provision of healthcare in the USA but most developed countries – and an increasing number of developing countries – attempt to provide universal healthcare for all their citizens. Even in the US, however, around 50% of the population's healthcare is met from public funds through programmes such as Medicare and Medicaid.
2. *Utilitarianism*, in its purest form, seeks to maximize social utility and is sometimes expressed as "the greatest good for the greatest number". In this approach expenditure on healthcare should be used to maximise population health as a whole. It asserts that adopting an intervention that is clinically or cost ineffective in one area of clinical practice will deprive other people, with other conditions, of cost effective care. Although emphasizing "efficiency", utilitarianism allows the interests of minorities to be over-ridden by majorities; and it does little to eradicate health inequalities.[9]
3. *Egalitarianism* postulates that, in healthcare, resources should be distributed in a manner that allows each individual to have a fair share of the opportunities available. It allows an adequate, but not necessarily a maximum, level of healthcare but raises difficult questions about what is fair and what is bad luck.[9]

The tensions between utilitarianism and egalitarianism can be overstated.[3,9] Many utilitarians accept that social values could (and should) be incorporated into decision-making. Qualified egalitarians also accept the concept of opportunity costs with all its moral implications. There is no formal synthesis, however, of these two latter theories of distributive justice. Both clash at some point with the convictions of many people; and each articulates ideas that most would be reluctant to relinquish.[3,9]

Figure shows the relationship between the likelihood of rejection of an intervention, on grounds of cost ineffectiveness, and the incremental cost effectiveness ration (ICER). Interventions with an ICER less than that at inflection A (£20,000 per QALY gained) would normally be expected to be considered cost effective. For interventions above inflection B (£30,000 per QALY gained) one or more social values would have to be taken into account for them to be considered cost effective and an appropriate use of healthcare resources. These particularly include the severity of the underlying condition (especially where there are no effective treatments), treatments that prolong life at the end of life, significant innovations whose impact might not have been fully captured in the clinical data, and

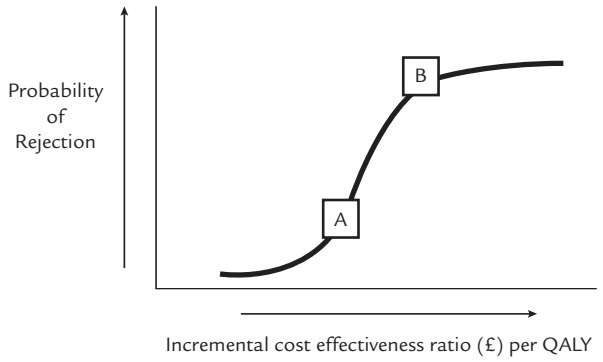

Figure. Relationship between the likelihood of rejection on grounds of cost ineffectiveness and the incremental cost effectiveness ratio (ICER).

disadvantaged populations. Indeed, all the interventions shown in Table 1 were considered, by NICE, to be an appropriate use of NHS resources and for those with ICERs of more than £30,000 per QALY gained it was social value judgements that proved to be the deciding factor.[10]

At the present, NICE's advisory bodies take a subjective approach to incorporating social value judgements into their decisions. In the future, however, at least some of them may be given quantitative weightings so as to ensure consistency as well as a greater degree of certainty.[11]

CONCLUSIONS

Decisions about the rational use of therapeutic interventions, in populations, require a robust approach to the appraisal of all the available clinical and economic evidence. This evidence, however, never supplants the need for decision-makers to take both scientific, and social value, judgements into account when making coverage decisions.

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